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<p>(21) International Application Number: <b>PCT/EP99/03677</b> (22) International Filing Date: <b>27 May 1999 (27.05.99)</b> (30) Priority Data: <b>60/086,895 27 May 1998 (27.05.98) US</b> (71) Applicant (for all designated States except US): <b>EUROCEL-TIQUE S.A. [LU/LU]; 122, boulevard de la Petrusse, Luxembourg (LU).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>FLEISCHER, Wolfgang [DE/DE]; Posener Strasse 6, D-55218 Ingelheim (DE). REIMER, Karen [DE/DE]; Im Rehwinkel 12, D-65582 Hambach (DE).</b> (74) Agent: <b>MAIWALD, Walter; Maiwald GmbH, Elisenhof - Elisenstrasse 3, D-80335 München (DE).</b></p>		<p>(81) Designated States: <b>AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: <b>PREPARATIONS FOR THE APPLICATION OF ANTI-INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE UPPER RESPIRATORY TRACT AND/OR THE EAR</b>  (57) Abstract  Use of anti-inflammatory agents such as povidone iodine for the preparation of a pharmaceutical composition for the treatment of diseases of the upper respiratory tract and/or the ear which are susceptible to the administration of such agents.</p>		

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Preparations for the application of anti-inflammatory, especially antiseptic agents and/or agents promoting the healing of wounds, to the upper respiratory tract and/or the ear

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The invention concerns preparations for the application of agents with anti-inflammatory, especially antiseptic and/or wound healing promoting properties to the upper respiratory tract and/or the ear. The preparations are specifically applied to wounds, skin, mucous membranes and mucosa-like unkeratinized epithelial, especially ciliary epithelial tissues in the upper respiratory tracts and/or the ears of humans and animals.

10

Furthermore, the invention concerns a method of preventing or treating infections by applying a pharmaceutical preparation.

15

A plurality of different antibiotic and antiseptic agents are known for the topical treatment of infectious maladies. A decisive disadvantage of antibiotic agents is that the infecting bacteria show primary resistances, and can acquire secondary resistances, against these agents. Further, antibiotics quite often lead to patient sensibilisation. The use of e.g. halogen-releasing antiseptics such as povidone iodine, also known as polyvidone iodine or PVP-iodine, i.e. the poly(1-vinyl-2-pyrrolidin-2-one)-iodine complex, can prevent resistances. Antiseptic agents are also much more rarely allergenic as compared to antibiotics.

20

At present, infectious diseases of the respiratory tract are treated with antibiotics. The application of antibiotic agents via the respiratory tract has been the subject of several reviews and articles with an emphasis, however, on the lower respiratory tract. Ramsey et al., for example, describe the intermittent administration of inhaled tobramycin in patients with cystic fibrosis in "The New England Journal

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of Medicine", Volume 340, Number 1, 1999, p. 23-30.

The aerosolization of imipenem/cilastatin for preventing pseudomonas-induced acute lung injury has been investigated by Wiener-Kronish in "Journal of  
5 Antimicrobiol Chemotherapy" (1996) 38, p. 809-818.

Pulmonary applications of different antibiotic agents, like benzyl penicillin, tobramycin or amikacin, for the treatment of infectious diseases are described by Schreier in several recent reviews, e.g. in "Medical applications of liposomes",  
10 Papahadjopoulos and Lasic (eds.), Elsevier 1998.

However, the treatment with antibiotics leads to the complications known to the skilled person. For example, patients suffering from acute or chronic laryngopharyngitis are often treated with antibiotics in order to alleviate the  
15 symptoms. This often merely leads to resistances of the bacteria responsible for the symptoms. Many diseases of the respiratory tract are caused by viruses. One typical example, in the upper respiratory tract, is rhinitis. Antibiotics are inefficient in such cases, and such patients are not cured of the infections.

20 The use of antiseptics and/or wound-healing promoting agents for external application to humans and animals is disclosed in our earlier patent EP 0 639 373. Specifically, liposome preparations of PVP-iodine are shown therein to be topically applicable to the external parts of the eye. These preparations generally take the form of a cream, an ointment, a lotion, a gel or a drop formulation.

25 Liposomes are well-known drug carriers and therefore the application of medicaments in liposomal form has been subject of investigation for quite some time. An overview concerning pulmonary delivery of liposome encapsulated drugs in asthma therapy is provided by the review "Pulmonary delivery of

liposomes" (H. Schreier, in "Journal of Controlled Release", 24, 1993, p.209-223).  
The physicochemical characterization of liposome aerosols and also their  
therapeutic applications to the respiratory tract are shown therein. Drugs that have  
been investigated for pulmonary delivery via liposomes include, e.g. anti-cancer  
5 agents, peptides, enzymes, anti-asthmatic and anti-allergic compounds and, as  
mentioned above, also antibiotics. The formulation of liposome aerosols or  
liposome powder aerosols using, for example a dry powder inhaler has also been  
described by H. Schreier in "Formulation and in vitro performance of liposome  
powder aerosols" (S.T.P. Pharma Sciences 4, 1994, p.38-44).

10

Although a lot of attention has been paid to liposomes as drug carriers, as can be  
seen from the cited documents, there appears to be no prior art relating to  
liposomes and other particulates as carriers of anti-inflammatory, especially  
antiseptic and/or wound-healing promoting agents for applications in the body,  
15 especially in the upper respiratory tract, including the mouth, throat and nose, and  
in the ear.

20

Most of the prior art cited above is concerned with liposome preparations. It  
should be understood that alternative drug carriers of a similarly particulate  
character exist. These drug carriers can often -and also in the context of this  
invention- be used instead of liposomes and include microspheres (generally  
comprising lipophilic polymers), nanoparticles, "Large Porous Particles" and  
individually coated drug substance molecules, e.g. made by using pulsed laser  
deposition (PLD) techniques. These PLD methods can be used to apply coatings  
25 to drug powders and to modify surface properties and release rate to a variety of  
drug systems.

Where hereinafter reference is made to liposomes or particulate carriers, it is to be  
understood that this is to incorporate such alternative carriers, too.

It is known in the art that the administration of inhalable particles to the respiratory tract can be achieved by nebulization or aerosolization of the liposome, microsphere, Large Porous Particle, PLD or nanoparticle preparations or by dry powder inhalation of the respective preparation.

5

There appears to be a marked reluctance in the art, to apply disinfectants to interior parts of the body, except maybe in extreme cases of life-threatening septical complications.

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Generally, antibiotic preparations appear to be preferred, even in view of their above-discussed disadvantages.

15

An object of the instant invention is to provide a well tolerated, easily applicable anti-inflammatory, especially antiseptic and/or wound-healing promoting preparation, which provides protracted release and protracted topical effect of the active agent in the lower respiratory tract.

20

According to the invention this object is attained in that the preparation comprises at least one anti-inflammatory, especially antiseptic and/or wound healing promoting agent in the form of a particulate carrier preparation, as defined in independent claim 1.

25

The invention further comprises a method of treating the upper respiratory tract, in humans and animals, as defined in independent claim 25.

The dependent claims define further advantageous embodiments of the invention.

In the context of the invention, the upper respiratory tract is considered to broadly include the mouth, nose and throat areas, down to and including the larynx and

excluding the external facial skin areas of mouth and nose. The upper respiratory tract thus comprises those parts which may be considered to be inside the body.

In the same context, the ear is considered to broadly include those parts of the ear which lie inside the skull, but are accessible from the outside thereof. Generally,

5 this will include the passages of the outer ear and, in some cases, the middle ear, but will exclude the inner ear and also those parts of the outer ear which surround the ear orifice, on the outside of the skull.

In the context of this invention, anti-inflammatory agents are understood to  
10 include antiseptic agents, antibiotic agents, corticosteroids, and wound-healing agents, as defined below.

In the context of this invention, antiseptic agents are understood to include those disinfecting agents which are pharmaceutically acceptable and suitable for the  
15 treatment of the upper respiratory tract to the extent that they can be formulated in accordance with the invention.

More specifically, antiseptic agents include inter alia oxygen- and halogen-releasing compounds; metal compounds, e.g. silver and mercury compounds;  
20 organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

25 Wound-healing agents comprise agents promoting granulation and epithelization such as dexpanthenol, allantoin, azulen, tannins, and vitamin B-type compounds.

The invention is premised on the surprising fact that particulate carriers, especially liposomes, but also microspheres, nanoparticles and coated drug substance molecules, are highly suited as carriers for antiseptic agents, especially for povidone iodine, and for agents promoting the healing of wounds, for application  
5 to the upper respiratory tract.

The preparations according to this invention permit protracted release of the agent or agents, and provide an extended and topical activity at the desired locus of action by interaction with cell surfaces.

10 The invention is, another aspect, based on a further surprising and unexpected fact. It is well known in the art that the formation of new body tissues may cause problems. Thus, it is known that body tissue repair may be accompanied by the formation of scar tissue, which can be functionally and/or cosmetically harmful, or  
15 at least undesirable. Hyperkeratosis and the uncontrolled proliferation of tissue may cause serious harm, leading to dysfunctions, and may of course also be cosmetically undesirable. After infections and inflammations, re-growing or healing tissue may cause neoplasms and intergrowth. It is thus well known in the art that in the curing of diseases, proper remodelling of tissue is not only  
20 desirable, but in fact necessary.

It has now been surprisingly found that the use of anti-inflammatory agents, singly or in combination with other such agents, leads to markedly less formation of undesirable body tissue in the course of tissue repair and other tissue growth  
25 processes. Thus, the formation of scar tissues is reduced, in skin but also in mucosa and in other tissues, such as muscle or inner organ tissues. Hyperkeratosis may be entirely suppressed, and intergrowth, or neoplasm formation in the curing of infective diseases is also highly reduced.



One object achieved by the invention is therefore concerned with improved tissue repair in the body. The invention achieves this by the application of anti-inflammatory agents, in the form of a particulate carrier preparation as defined in the independent claims.

5

The anti-inflammatory, antiseptic and/or wound-healing preparation can be administered to the respiratory tract by a nebulization agent loaded of the particulate carrier preparation, or by dry powder inhalation of the respective preparation. For example, a liposome preparation can be made by loading  
10 liposomes with PVP iodine in a conventional procedure.

It is also possible to compact the loaded liposomes, optionally together with auxiliary materials, such as low molecular sugars, preferably lactose, to a tightly compacted solid medicament reservoir. This medicament stock can then be  
15 abraded or micronized or treated in other ways to yield the powder in particle form. The resulting liposome preparation can be administered by inhalation of the preparation in the form of a powder aerosol, as, for example, described in "Acute Effects of Liposome Aerosol Inhalation on Pulmonary Function in Healthy Human Volunteers" (Thomas et al., Preliminary report, Volume 99, 1991, p. 1268-1270).  
20 The pressures for preparing the tightly compacted solid medicament stock are preferably in the range of from 50-500 MPa. Such medicament stock is described in WO 94/14490 and a device for administration is disclosed in WO 93/24165.

The nature or constitution of the liposomes is generally not critical. The liposome  
25 preparation as, for example, described in EP 0 639 373 can be administered to the nose or the throat as an aerosol, e.g. a pump spray. For applications in the mouth cavity, the inventive preparations are preferably formulated as a pump spray, a gel, or a rinsing solution. The disclosure of EP 0 639 373 is incorporated by reference.

The preparations according to this invention apparently do not only contain the active agent, like povidone iodine, encapsulated in the particulate carrier, especially in liposomes. It seems that there is also some amount of agent which is not contained inside the carrier. The preparations according to the invention often  
5 show a marked initial effect which is observed in addition to the slower, protracted release of the active agent from the carrier. This effect is especially observed where the carrier comprises liposomes. Without wishing to be bound to any theoretical explanation, it is presently assumed that in addition to active agent encapsulated inside the liposomes, some active agent is present outside of the  
10 liposomes, and probably loosely bound to the outer surfaces of the liposomes. This could be due to association of active agent molecules with the liposomal membrane, or it could be due to active agent molecules forming a layer on the liposomal surface, which layer partly or even fully coats the liposome externally. The type and amount of this initial agent effect can e.g. be influenced by choice  
15 of the concentration parameters.

The amphiphilic substances generally known in prior art to form liposome membranes can be employed in the context of the invention as long as they are pharmaceutically acceptable for the intended application. Presently, liposome  
20 forming systems comprising lecithin are preferred. Such systems can comprise hydrogenated soy bean lecithin besides cholesterol and disodium succinate-hexahydrate; it is presently specifically preferred to use hydrogenated soy bean lecithin as the sole membrane-forming agent.

25 The known prior art methods for forming liposome structures are described in the documents cited above and can generally be used in the context of the invention. Broadly, these methods comprise mechanical agitation of a suitable mixture containing the membrane forming substance and water or an aqueous solution. Filtration through suitable membranes is preferred in forming a substantially

uniform liposome size.

The average size of the liposomes according to this invention can vary over a broad range, generally from about 1 to about 20,000 nm. Liposomes with  
5 diameters in the range of about 50 and 4,000 nm are preferred. Liposomes with diameters at around 1000 nm are presently most preferred for e.g. gel applications. For solutions, smaller average diameters may be more suitable.

Where alternative particulate carriers are used, they are generally prepared as  
10 known in the art. Thus, microspheres which are used to deliver a very wide range of therapeutic or cosmetic agents, are made as described for example in WO 95/15118.

Nanoparticles may in some cases be used, provided that they can be loaded with a  
15 sufficient amount of active agent and can be administered to the lower respiratory tract according to this invention. They can be prepared according to the methods known in the art, as e.g. described by Heyder (GSF München) in "Drugs delivered to the lung, Abstracts IV, Hilton Head Island Conference, May 1998.

20 Methods using a pulse laser deposition (PLD) apparatus and a polymeric target to apply coatings to drug powders in a short non-aqueous process are also suitable for the formation of particulate preparations according to this invention. These have e.g. been described by Talton et al., "Novel Coating Method for Improved Dry Delivery", Univ. of Florida UF 1887 (1998).

25 A further suitable delivery system employs Large Porous Particles as disclosed by David A. Edwards et al. in "Large Porous Particles for Pulmonary Drug Delivery" (Science, 20. June 1997, Vol. 276, p 1868-1871).

Preferred anti-inflammatory agents comprise antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents, as single substances or in combination with each other.

5 Preferred antiseptic agents comprise the well-known pharmaceutical substances providing fast effect, a broad range of activity, low systemic toxicity and good tissue compatibility. They can e.g. be selected from the group comprising metal compounds, phenolic compounds, detergents, iodine and iodine complexes. A specifically preferred antiseptic agent is povidone iodine.

10

Preferred agents promoting the healing of wounds comprise substances which have been described in the literature for such application. Preferred such agents include substances known to promote epithelisation. These include vitamins, specifically from the vitamin B group, allantoin, some azulenes etc.

15

Some presently highly preferred embodiments of the invention comprise anti-inflammatory agents or combinations of such agents which show beneficial effects in tissue repair, especially with respect to functional and cosmetic tissue remodelling. In these embodiments, the active agent is often an antiseptic, such as PVP-iodine, or an antibiotic.

20

In preferred embodiments, the invention's preparations containing anti-inflammatory, especially antiseptic and/or wound-healing promoting agents can comprise further agents such as anaesthetic agents. Inventive preparations can also contain customary further agents, including adjuvants and additives, antioxidants, conserving agents or consistency-forming agents such as viscosity adjusting additives, emulgators etc.

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Generally, the concentrations in the preparation, particle sizes, active agent loadings etc. will be selected for such alternative carriers to correspond basically to the parameters discussed herein with respect to liposome preparations. Selecting and providing such parameter based inter alia on straightforward experimentation, is well within the skill of an ordinary worker experienced in this art.

A presently highly preferred use of the inventive liposome preparations is in the local treatment of infections of the nose, mouth and throat, especially when the liposome preparations contain povidone iodine. Also in this indication, the inventive antiseptic preparations, especially those containing PVP iodine, have the great advantage of not causing resistances and lead to much less allergic reactions, while permitting a very cost-efficient therapy with a broad spectrum of effect. A povidone iodine liposome preparation according to this invention is e.g. effective against viruses, such as herpes simplex. This effect is not provided by antibiotic agents. Further, a liposome preparation of a microbicidal agent such as povidone iodine provides protracted release of the agent from liposomes in the nasal or oral mucosa. This leads to extended effect of the antimicrobial substance, and thus less frequent application, as compared with the customary antiseptic solution preparations.

The present invention is also useful in the treatment of infectious diseases or for alleviation of diseases such as HIV infections which are accompanied by opportunistic infections. Also patients having a suppressed immune system, for example, after organ transplants, can be treated according to the invention. In particular, acute and chronic laryngopharyngitis and angina can be treated with the povidone iodine preparation according to the invention.

Further highly preferred use is in tissue repair, especially in functional and cosmetic tissue remodelling.

5 Preparations according to this invention can take a variety of forms, which are suitable for administration via the upper respiratory tract and the ear, including pharmaceutically acceptable solid or liquid formulations. Preparations according to this invention can be therefore in the form of (powder) aerosol or in the form of a compacted solid medicament reservoir, preferably a ring tablet, more preferably a gelatine capsule, a powder, a spray, an emulsion, a dispersion, a suspension or a solution containing the carrier and agent or agents. They can be in the form of a gel, or some other semi-solid, viscous or solid application form, e.g. for application in the mouth cavity.

15 Generally, the amount of active agents in an inventive preparation will be determined by the desired effect, on the one hand, and the carrying capacity of the carrier preparation for the agent, on the other hand.

20 For inventive preparations with large amounts of active agents or high dosages of active agent, solid, liquid or gel preparations are often preferred to nebulized preparations or aerosols, or to powders or powder aerosols. Broadly, the amount of active agent in an inventive carrier preparation can range in concentrations between the lower limit of effectiveness of the agent and the maximum loading of the agent in the respective carrier preparation.

25 More specifically, for an antiseptic agent, such as povidone iodine, a solution or dispersion in an inventive carrier preparation, especially where the carrier is a liposome preparation, can contain between 0.1 and 10 g of agent in 100 g of preparation. Such a preparation will then typically contain between 1 and 5 g of liposome membrane-forming substance, especially lecithin, per 100 g of

preparation.

In a lotion, which can be a hydrophilic or a lipophilic lotion, a typical range of active agent will be between 0.5 and 10 g agent, and between 1 and 5 g, preferably about 4 g of liposome membrane forming agent such as hydrogenated soy bean lecithine, per 100 g of lotion. In the case of a hydrophilic lotion, electrolyte solution will often be used in preparing the liposome containing lotion. A lipophilic lotion will often be made from agent, membrane forming substance and lipophilic formation agents such as medium chain length triglycerides etc.

10

A hydrophilic cream comprising an inventive liposome preparation will generally comprise between 0.1 and 10 g agent, such as povidone iodine, together with between about 1 and 10 g membrane forming substance and further typical O/W cream forming additives, per 100 g of cream.

15

A comparable amphiphilic cream according to the invention will have similar contents of agent and membrane forming substance such as lecithine, and will have the typical further additives of an amphiphilic cream.

20 A hydrophilic ointment according to the invention can broadly comprise between 0.1 and 10 g agent and between 1 and 10 g liposome membrane forming substance such as lecithine, together with typical prior art ointment basis substances such as Macrogol (TM) and water, in 100 g of ointment.

25 A non-alcoholic hydrogel according to the invention could broadly comprise between 1 and 5 g agent such as povidone iodine, approximately 2 g lecithine and gel forming substances such as Carbopol (TM), with pH-adjusting agent and water to form 100 g of hydrogel.

An inventive aerosol or spray preparation will often comprise up to 50 mg, but could comprise up to and above 100 mg of liposomal active agent formulation, per unit spray dose. The spray preparation will typically comprise at least 10 % wt of active agent such as PVP-Iodine in the loaded liposomes (or  
5 alternative carrier particles), but may comprise up to 50 % wt or even more of active agent. Where the active agent is PVP-Iodine, the amount of available iodine will generally be about 10 % wt (based on PVP-Iodine).

10 More specific formulations are notable from the embodiment examples.

The features and advantages of this invention will become notable in more detail from the ensuing description of preferred embodiments. In these embodiments which include a best mode, povidone iodine is exemplified as an antiseptic agent and liposomes are chosen as the carrier. This should, however, not be construed  
15 as a restriction of this invention to antiseptic agents or, among antiseptic agents, to povidone iodine, and/or to liposomes as the carrier, although such preparations are specifically preferred.

20 One preferred method for producing the invention's liposomes can generally be described as follows:

The lipid membrane-forming components, e.g. lecithine, are dissolved in a suitable solvent such as chloroform or a 2:1 mixture of methanol and chloroform and are filtered under sterile conditions. Then, a lipid film is produced on a sterile high  
25 surface substrate, such as glass beads, by controlled evaporation of the solvent. In some cases, it can be quite sufficient to form the film on the inner surface of the vessel used in evaporating the solvent, without using a specific substrate to increase the surface.



An aqueous system is prepared from electrolyte components and the (one or more) active agents to be incorporated in the liposome preparation. Such an aqueous system can e.g. comprise 10 mmol/l sodium hydrogen phosphate and 0.9 % sodium chloride, at pH 7.4; the aqueous system will further comprise at least the  
5 desired amount of the active agent, which in the embodiment examples is povidone iodide. Often, the aqueous system will comprise an excess amount of agent or agents.

The liposomes are generally formed by agitating said aqueous system in the  
10 presence of said film formed by the lipid components. At this stage, further additives can be added to improve liposome formation; e.g. sodium cholate can be added. Liposome formation can also be influenced by mechanical action such as pressure filtration through e.g. polycarbonate membranes, or centrifuging. Generally, the raw liposome dispersion will be washed, e.g. with electrolyte  
15 solution as used in preparing the above-described solution of the active agent.

When liposomes with the required size distribution have been obtained and washed, they can be redispersed in an electrolyte solution as already described, often also comprising sugars such as saccharose or a suitable sugar substitute.  
20 The dispersion can be freeze-dried, and it can be lyophilysed. It can, prior to use, be reconstituted by addition of water and suitable mechanical agitation at the transition temperature of the lipid component, which for hydrogenated soy bean lecithine is e.g. 55°C.

25 In the following Examples, hydrogenated soy bean lecithine (EPIKURON (TM) 200 SH obtainable from Lukas Meyer, Germany or PHOSPOLIPON (TM) 90 H obtainable from Nattermann Phospholipid GmbH, Germany) was used. However, other pharmaceutically acceptable liposome membrane forming substances can be used instead, and the person skilled in the art will find it easy to select suitable

alternative liposome forming systems from what is described in prior art.

Embodiment Example I

5 In a 1000 ml glass flask, provided with glass beads for increased surface, 51.9 mg cholesterol and 213 mg hydrogenated soy bean lecithine were dissolved in a sufficient amount of a mixture of methanol and chloroform in a 2:1 ratio. The solvent was then evaporated under a vacuum until a film was formed on the inner surface of the flask and on the glass beads.

10 2.4 g PVP iodine (containing about 10 % available iodine) were separately dissolved in 12 ml water.

Again in a separate vessel, 8.77 g sodium chloride and 1.78 g  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$   
15 were dissolved in 400 ml water. Further water was added up to a total volume of 980 ml, and then, approximately 12 ml 1N hydrochloric acid were added to adjust pH to 7.4. This solution was then topped up with water to exactly 1000 ml.

In a fourth vessel, 900 mg saccharose and 57 mg disodium succinate were  
20 dissolved in 12 ml water.

The PVP iodine solution was then added to the lipid film in the flask and the mixture was shaken until the film dissolved. This produced liposome formation from the hydrated lipids in the flask. The product was centrifuged and the  
25 supernatant liquid was discarded. The saccharose solution was added ad 12 ml and the product was again centrifuged. Afterwards the supernatant liquid was again discarded. At this stage, a further washing step, using the saccharose solution or the sodium chloride buffer solution could be used.

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After the last centrifugation step and discarding of the supernatant, sodium chloride buffer solution was added ad 12 ml, and the liposomes were homogenously distributed therein. The product was then distributed into vials each containing 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step.

After the freeze-drying, each vial comprised about 40 mg solids.

The method of Embodiment Example I has a minor disadvantage in that the PVP iodine solution used, due to the high percentage of solids, is rather viscous and thus more difficult to handle.

#### Embodiment Example II

In a 2000 ml flask provided with glass beads to increase surface, 173 mg hydrogenated soy bean lecithine and 90 mg disodium succinate were dissolved in approximately 60 ml of a methanol/chloroform mix in a 2:1 ratio. The solvent was removed under vacuum until a film was formed.

4 g PVP iodine (10 % available iodine) were dissolved in 40 ml of the sodium chloride buffer solution described in Embodiment Example I, and were added to the lipid film in the flask. The flask was then shaken until the film dissolved and liposomes were formed.

The product was centrifuged and the supernatant liquid was discarded.

To the thus produced liposome pellet, further sodium chloride buffer solution was added ad 40 ml, and the centrifuging step was repeated. The supernatant was again discarded. At this stage, this washing step could be repeated where

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necessary.

After the final centrifuging and decanting step, sodium chloride buffer solution was again added to the precipitated liposomes ad 40 ml. The homogenous  
5 dispersion was then distributed into vials, each vial containing about 2 ml liposome dispersion, and the vials were then subjected to a freeze-drying step. This produced approximately 200 mg freeze-dried solids per vial.

From the freeze-dried solids of Examples I and II, further preparations were made  
10 as described in subsequent Embodiment Examples and Test Reports.

Like that of Embodiment Example I, the above-described method uses a hydrating step after film formation in the presence of organic solvents and aims at inclusion rates of 5 bis 15 %. These methods generally produce rather large and often  
15 multi-lamellar liposomes.

The above-described methods can be modified by a high pressure filtering step through a suitable membrane such as a polycarbonate membrane after the raw liposomes have been formed or after any of the subsequent washing steps or  
20 directly by using high pressure homogenisation. This produces much smaller, unilamellar liposomes at increased amounts of encapsulated agent.

Instead of high pressure homogenisation, other prior art methods known to provide small uniform sized liposomes can be employed.

25

### Embodiment Example III

A hydrophilic (O/W) cream was prepared from 10 g hydrogenated soy bean lecithine/PVP iodine liposomes as described in Embodiment Example II; these

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were mixed with 4 g Polysorbate 40 (TM), 8 g cetylstearyl alcohol, 8 g glycerol, 24 g white vaseline, and water ad 100 g.

#### Embodiment Example IV

5

An amphiphilic cream was prepared from 10 g hydrogenated soy bean lecithine/povidone iodine liposomes as described in Embodiment Example II; 7.5 g medium chain length tryglyceride, 7 g polyoxyethyleneglycerol monostearate, 6 g cetylstearyl alcohol, 8 g propylene glycol, 25 g white vaseline, and water ad 100 g.

10

#### Embodiment Example V

A hydrophilic ointment which can be rinsed off with water was prepared using 10 g of liposomal PVP iodine as described in Embodiment Example II, 55 g Macrogol 400 (TM), 25 g Macrogol 4000 (TM), and water ad 100 g.

15

#### Embodiment Example VI

A hydrogel was prepared from 4 g liposomal PVP iodine as described in Embodiment Example II, 0.5 g Carbopol 980 NF (TM), sodium hydroxide ad pH 7, water ad 100 g.

20

Further modifications of the above-described embodiments are envisaged.

25

Thus, the creams of Embodiment Examples III and IV can have an additional content of an agent known to promote the healing of wounds, such as allantoin. Such an agent will be added in a pharmaceutically useful concentration, in the case of allantoin in the range of 0.1 to 0.5 g, per 100 g of cream. The wound-

- 20 -

healing agent can be incorporated in the cream base, in which case it will largely be outside the liposomes. It can, however, be partly or mostly incorporated in the liposomes, in which case it will be added at a corresponding suitable stage of the liposome preparation method.

5

Similar alternatives are easily envisaged on the basis of the further Embodiment Examples.

10

It is also possible to prepare embodiments similar to the above described ones, which comprise an agent capable of promoting the healing of wounds instead of, and not in addition to, the antiseptic agent as e.g. povidone iodine disclosed in the above Embodiment Examples. Presently, it is however preferred to use a wound healing promoting agent (if at all) in addition to an antiseptic agent.

15

For application of the inventive preparations to a patient, known systems can be used, such as pneumatic pump applicators, two-chamber gas pressure packs, aerosol spray dispensers etc.

20

In a pneumatic pump applicator, a bellows device is provided between an upstream and a downstream valve, both valves operating one way in the same direction. A supply of pharmaceutical preparation, such as an ointment or gel, is contained in a reservoir upstream of the valves- and -bellows device.

25

When compressing the bellows, the downstream valve opens and permits a dosed amount of preparation to leave the device for application. When the bellows is extended, this valve shuts and prevents reentry of the preparation. At the same time, the upstream valve opens and permits preparation from the reservoir to enter into the bellows, for release through the downstream valve upon the next compression step of the bellows.

The reservoir is sealed by a closure element which can move through the reservoir like a piston moves in a cylinder. By the stepwise emptying of the reservoir, this closure element is sucked into the reservoir, so that the remaining amount of pharmaceutical preparation in the reservoir is always sealed off, while at the same  
5 time the reservoir can be emptied.

Such a device is useful for pasty preparations, creams, ointments etc.

In a two-chamber gas pressure pack, the pharmaceutical preparation is contained  
10 in a bag of flexible plastics film material. Often, this is high pressure polyethylene.

The bag is contained inside a gas tight pressure vessel which further contains a supply of pressurizing gas, very often a compressed inert gas like nitrogen or air.  
15

The plastic film bag has only one outlet, which is gas-tightly connected to the interior wall of the pressure vessel, surrounding a single opening thereof. The pressurized gas in the vessel tends to compress the bag, driving the pharmaceutical preparation inside the bag out through the opening of the bag and thus through the  
20 opening of the vessel. A valve and, in case, spray-head device is provided in the vessel mouth. Operating the valve releases a spray mist, a jet of liquid or a portion of flowable solid such as cream. Using such a system, solutions, emulsions, creams, ointments and gels can be dosed and applied.

25 Using inventive preparations efficiency tests were then carried out, as follows:

### Test I

This was an in-vitro-test of the bactericidal effect provided by an inventive povidone iodine liposome preparation. The test was based on the quantitative  
5 suspension test as described in "Richtlinien der Deutschen Gesellschaft für Hygiene und Mikrobiologie", 1989. In this test, the bactericidal agent is used to kill staphylococcus aureus (ATCC 29213), a major problem in hospital hygiene.

The liposome preparation used was that of Embodiment Example I. At different  
10 contact times between 1 und 120 minutes, the minimum concentration of the preparation in water was determined which was capable of killing the staphylococci.

The results are shown in Table 1.

15

TABLE I

	<u>Contact Time (Minutes)</u>	<u>Bactericidal Concentration</u>
	1, 2, 3, 4	≥ 0.060 %
	5, 30, 60	≥ 0.015 %
20	120	≥ 0.007 %

The results show that at short contact times (between 1 and 4 minutes) the bactericidal concentration is as low as 0.06 % and that at long contact times (120  
minutes) the bactericidal concentration can be as low as 0.007 %.

25

### Test II

The virucidal and chlamydicidal activity of liposomal PVP-iodine has been studied, in cell cultures, by Wutzler et al., 9th European Congress for Clinic



Microbiology and Infection Diseases, Berlin, March 1999. In cell cultures, liposomal PVP-iodine is highly effective against herpes simplex virus type 1 and adenovirus type 8, while the long-term cytotoxicity experiments indicated that the liposomal form is better tolerated than aqueous PVP-iodine by the majority of cell lines tested. PVP-iodine in liposomal form is not genotoxic.

### Test III

A 3% PVP-iodine hydrogel liposomal preparation was compared with a 3% PVP-iodine ointment, where the active agent was not in liposomal form. The agent was applied to standardized in vitro cultures of rat skin and peritoneal explants, as a screening for tissue compatibility of skin and wound antiinfectives.

The growth rate of the cultured explants was studied after 30 minutes exposure and incubation with a test substance.

Again, the substantially better toleration of the liposomal preparation was clearly shown in the results, in terms of peritoneum growth rate and skin growth rate.

With the ointment, the peritoneum growth rate reached 85%, and the skin growth rate reached 90%; with the liposomal hydrogel formulation, the peritoneum growth rate was 96%, and the skin growth rate was 108%; these values are to be compared with 100% values in a control test using Ringer's solution as the agent.

### Test IV

The toleration of liposomal PVP-iodine solutions for nasal applications was studied by investigating the influence of different test substances on ciliated epithelium cells, the most sensible cells of the mucous membrane. A cytotoxic

damage of these cells which would cause a restriction of the mucociliar clearance can be determined by a detectable decrease of the ciliary vibration.

5 Human ciliated epithelium cells were analysed by an in-vitro method which enables the determination of the ciliary activity or ciliary vibration. The corresponding cells were exposed and incubated with 100 µl test substance at a temperature of 37°C. After an incubation period of 5 minutes the ciliary vibration was measured.

10 By using this in-vitro method a nutrient solution (Dulbecco) as standard, a 0.2% chlorohexidine solution (typical antiseptic agent), conventional polyvidone iodine solutions (Betaisodona ®) of different concentrations (5.0%, 2.5% and 1.25% PVP-iodine) and a liposomal solution containing 4.5% of PVP-iodine were tested.

15 The substantially better toleration of the liposomal preparation was clearly shown in the results: if the ciliated epithelium cells were exposed to the Betaisodona solutions containing 5.0% or 2.5% PVP-iodine, no ciliary activity could be observed after the incubation period. Treating the cells with a chlorohexidine solution led to a decrease of the measured ciliary vibration in comparison to the  
20 standard (nutrient solution). The low concentrated Betaisodona solution containing 1.25% PVP-iodine, didn't cause a detectable decrease of the ciliary activity. With respect to the measured ciliary vibration no differences to the standard (nutrient solution) could be determined by exposing the human ciliated epithelium cells to the concentrated liposomal 4.5% PVP-iodine solution.

25 These results indicate that the liposomal formulation is well tolerated for nasal application and advantageous with respect to for e.g. chlorohexidine or conventional Betaisodona solutions.

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Claims

1. A process for the manufacture of a pharmaceutical preparation for the application of anti-inflammatory, especially antiseptic agents and/or agents  
5 which promote the healing of wounds to the upper respiratory tract and/or the ear, characterised in that the preparation contains at least one of said agents combined with a particulate carrier.
2. The process of claim 1,  
10 characterised in that said particulate carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation, or a laser-pulse polymer coated molecule preparation.
3. The process according to claim 1 or 2,  
15 characterised in that at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.
4. The process of any one of claims 1 to 3,  
characterised in that the anti-inflammatory agent is an antiseptic agent, an  
20 antibiotic, a corticosteroid, or a wound-healing promoting agent.

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5. The process of any one of claims 1 to 4,  
characterised in that the antiseptic agent is selected from oxygen- and halogen-  
releasing compounds; metal compounds, such as silver and mercury compounds;  
organic disinfectants including inter alia formaldehyde-releasing compounds,  
5 alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols,  
quinolines and acridines, hexahydropyrimidines, quaternary ammonium  
compounds and iminium salts, and guanidines.

6. The process according to claim 5,  
10 characterised in that the antiseptic agent is selected from the group comprising  
metal compounds such as mercury compounds, phenol derivatives such as thymol,  
eugenol and hexachlorophene, iodine and iodine complexes.

7. The process according to claim 6,  
15 characterised in that the antiseptic agent is povidone iodine.

8. The process according to any one of claims 1 to 7,  
characterised in that the wound-healing promoting agent is selected from agents  
promoting granulation and epithelization such as dexpanthenol, allantoines,  
20 azulenes, tannines, compounds from the vitamin B series, or similarly acting  
agents.

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9. The process according to any one of the preceding claims, characterised in that the preparation contains at least one antiseptic and at least one wound-healing promoting agent.

5 10. The process according to any one of the preceding claims, characterised in that the carrier particles, especially liposomes, have a substantially uniform size in the range between about 20 and about 20,000 nm, preferably in the range between about 50 and about 4,000 nm, more preferably between 500 and 2,500 nm and especially preferably a uniform size of about 1,000 nm  
10 diameter.

11. The process according to any one of the preceding claims, characterised in that the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours  
15 duration.

12. The process according to claim 11, characterised in that the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

20

13. The process according to any one of the preceding claims, characterised in that the preparation additionally comprises at least one

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anaesthetically active agent.

14. The process according to any one of the preceding claims,  
characterised in that the preparation contains additives and adjuvants such as  
5 conserving agents, antioxidants and consistency-forming additives.

15. The process according to any one of claims 1 to 14, the preparation  
being in the form of a solution or dispersion comprising the active-agent loaded  
carrier, especially in the form of liposomes, preferably in the form of a liquid  
10 pharmaceutical preparation.

16. The process according to any one of claims 1 to 14, the preparation  
being in the form of a hydrophilic or amphiphilic cream, comprising the carrier  
and agent formulation in a hydrophilic or amphiphilic cream base, or in the form  
15 of a pharmaceutical O/W or W/O lotion.

17. The process according to any one of claims 1 to 14, the preparation  
being in the form of a pharmaceutical ointment, containing the carrier and agent  
or agents in a pharmaceutical ointment base.

20

18. The process according to any one of claims 1 to 14, the preparation being in the form of a pharmaceutical gel, especially a non- alcoholic hydrogel containing the carrier and agent or agents in a pharmaceutically acceptable hydrogel basis.

5

19. The process according to any one of claims 1 to 14, the preparation being in the form of a spray containing the carrier and agent in a pharmaceutically acceptable sprayable solid or liquid formulation.

10

20. The process according to any one of the preceding claims, the preparation being in the form of a pharmaceutical solution or dispersion formulation, which comprises:

a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and

15

b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

wherein the liposomes are of substantially uniform size between about 50 and about 4,000 nm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical solution or dispersion formulation.

20

21. The process according to claim 20,  
characterised in that the liposomes are of substantially uniform size, with  
diameters at around 1,000 nm, and the formulation is a gel.
- 5           22. The process according to any one of claims 1 to 21, wherein the  
preparation is suited for the treatment of infectious diseases or alleviation of  
diseases such as HIV infections which are accompanied by opportunistic infections  
or a suppressed immune system.
- 10           23. The process according to any one of claims 1 to 21, wherein the  
preparation is suited for the treatment of acute and/or chronic laryngopharyngitis,  
angina and/or rhinitis.
- 15           24. The process according to any one of claims 1 to 21, wherein the  
preparation is suited for functional and cosmetic tissue remodelling and repair  
treatments.
- 20           25. A method of preventing or treating infections and/or of functional  
and cosmetic tissue remodelling and repair, of the human or animal upper  
respiratory tract and/or ear, by applying, to said tract and/or ear, a pharmaceutical  
preparation comprising at least one anti-inflammatory, especially antiseptic agent  
and/or wound-healing promoting agent, said at least one agent being combined



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with a particulate carrier in said preparation.

26. The method of claim 25, wherein said carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a  
5 Large Porous Particle preparation or a laser-pulse polymer coated molecule preparation.

27. The method of claim 25, wherein at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere  
10 carrier.

28. The method of claim 25, wherein the anti-inflammatory agent is selected from antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents.

15 29. The method of claim 25, wherein the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as  
20 halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

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30. The method of claim 25, wherein the antiseptic agent is selected from the group comprising metal compounds such as mercury compounds phenol derivatives such as thymol, eugenol and hexachlorophene, iodine and iodine complexes.

5

31. The method of claim 25, wherein the antiseptic agent is povidone iodine.

10

32. The method of claim 25, wherein the wound-healing promoting agent is selected from agents promoting granulation and epithelization such as dexpanthenol, allantoines, azulenes, tannines, compounds from the vitamin B series or similarly acting agents.

15

33. The method of claim 25, wherein the preparation contains at least one antiseptic and at least one wound-healing promoting agent.

20

34. The method of claim 25, wherein the carrier particles, especially liposomes, have a substantially uniform size in the range between about 20 and about 20,000 nm, preferably in the range between about 50 and about 4,000 nm, more preferably between 500 and 2,500 nm and especially preferably a uniform size of about 1,000 nm diameter.

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35. The method of claim 25, wherein the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

5        36. The method of claim 25, wherein the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

10       37. The method of claim 25, wherein the preparation additionally comprises at least one anaesthetically active agent.

38. The method of claim 25, wherein the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

15

39. The method of claim 25, the preparation being in the form of a solution or dispersion comprising the active-agent loaded carrier, especially in the form of liposomes, preferably in the form of a liquid pharmaceutical preparation.

20       40. The method of claim 25, the preparation being in the form of a hydrophilic or amphiphilic cream, comprising the carrier and agent formulation in a hydrophilic or amphiphilic cream base, or in the form of a pharmaceutical O/W

or W/O lotion.

41. The method of claim 25, the preparation being in the form of a pharmaceutical ointment, containing the carrier and agent or agents in a pharmaceutical ointment base.

42. The method of claim 25, the preparation being in the form of a pharmaceutical gel, especially a non- alcoholic hydrogel containing the carrier and agent or agents in a pharmaceutically acceptable hydrogel basis.

10

43. The method of claim 25, the preparation being in the form of a spray containing the carrier and agent in a pharmaceutically acceptable sprayable solid or liquid formulation.

15

44. The method of claim 25, the preparation being in the form of a pharmaceutical solution or dispersion formulation, which comprises:

- a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and
- b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

20

wherein the liposomes are of substantially uniform size between about 50

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and about 4,000 nm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical solution or dispersion formulation.

5           45.   The method of claim 25, wherein the liposomes are of substantially uniform size, with diameters at around 1,000 nm, and the preparation is a gel.

          46.   The method of claim 25, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections  
10       which are accompanied by opportunistic infections or a suppressed immune system.

          47.   The method of claim 25, wherein the preparation is suited for the treatment of laryngopharyngitis, angina and/or rhinitis.

15

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/03677

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 639 373 A (EUROCELTIQUE) 22 February 1995 (1995-02-22) claims 1-18	1-47
X	EP 0 613 685 A (GONZALEZ ENSENAT, PEDRO, ET AL.) 7 September 1994 (1994-09-07)  claim 1 column 4, line 19 - line 26  -/-	1-5, 10-12, 14-19, 22-29, 34-36, 38-47

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 October 1999

Date of mailing of the international search report

09/11/1999

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## INTERNATIONAL SEARCH REPORT

Internati Application No  
PCT/EP 99/03677

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 509 338 A (MERZ & CO.) 21 October 1992 (1992-10-21)  claims 1,9 example 7	1-5, 10-12, 14-19, 22, 25-30, 34-36, 38-43, 45-47
X	CHEMICAL ABSTRACTS, vol. 117, no. 10, 7 September 1992 (1992-09-07) Columbus, Ohio, US; abstract no. 97244, GILBERT, BRIAN E. ET AL: "Aerosolized liposomal amphotericin B for treatment of pulmonary and systemic Cryptococcus neoformans infections in mice" XP002119931 abstract & ANTIMICROB. AGENTS CHEMOTHER. (1992), 36(7), 1466-71, 1992,	1-4, 10-12, 15,19, 22, 25-28, 34-36, 38,39, 43,46

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/03677

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 25-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03677

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